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Relationship between the severity of alcoholic liver cirrhosis and the metabolism of caffeine in 226 patients

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Key words
caffeine – metabolism – alcoholic cirrhosis

Abbreviations
137X = caffeine,
17X = 1-7 dimethylxanthine,
13X = 1-3 dimethylxanthine,
13U = 1-3 dimethylurate,
37X = 3-7 dimethylxanthine,
17U = 1-7 dimethylurate,
1X = 1-methylxanthine,
1U = 1-methylurate,
7X = 7-methylxanthine,
3X = 3-methylxanthine,
AFMU = 5-acetylamino-6-formylamino-3-methyluracyl.
SA = slow acetylators
RA = rapid acetylators

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Abstract. Objectives: To evaluate the polygenic regulated caffeine metabolism in a group of 226 patients with liver alcoholic cirrhosis classified according to the Child score. Methods: Over a 14-year period an hepatic function test, using caffeine as probe drug, has been systematically associated to the usual clinical and biochemical investigations performed in patients with liver alcoholic cirrhosis. "Caffeine test" consisted in a 200 mg caffeine oral intake. Urines were collected over 24 hours: caffeine (137X), 1-7 dimethylxanthine (17X), 1-3 dimethylxanthine (13X), 1-3 dimethylurate (13U), 3-7 dimethylxanthine (37X), 1-7 dimethylurate (17U), 1-methylxanthine (1X), 1-methylurate (1U), 7-methylxanthine (7X), 3-methylxanthine (3X), and 5-acetylamino-6-formylamino-3-methyluracyl (AFMU) were analyzed by high performance liquid chromatography (HPLC). Total and individual metabolite urinary elimination rates were expressed in µmol/24 hours. Enzyme activities were evaluated from the following urinary metabolites ratios: (AFMU+1U+1X)/17U for CYP1A2, 17U/17X for CYP2A6, AFMU/(AFMU+1U+1X) for NAT-2, 1U/1X for XO. Results: Compared to healthy subjects, whatever the Child score, caffeine metabolism was reduced by half in patients with alcoholic cirrhosis. The main cause was the decreased CYP1A2 activity. On the other hand, XO and CYP2A6 activities were increased and NAT-2 activity remained unchanged in slow acetylators (SA) and decreased in rapid acetylators (RA) Child B and C. Bimodality of NAT-2 distribution was unclear, but a right assignment of RA and SA phenotype in cirrhotic patients, confirmed by comparison with genotype, was obtained, using the antimode value of NAT-2 distribution used in healthy subjects. At last, there was an interindividual variability in caffeine metabolism as great as in the usual laboratory parameters. Conclusion: Metabolism of caffeine is decreased in patients with alcoholic liver cirrhosis. This decrease paralleled the modifications of the usual laboratory tests and does not bring additional information on the severity of the disease. But the equilibrium between the various metabolic pathways of caffeine is impaired. Beyond the changes of a specific enzymatic activity, this must be taken into account particularly for drugs whose metabolism is of the polygenic regulation type.

Introduction

It is now well established that drug metabolism is the main source of variability of patient response to recommended dosage regimens [Alvan et al. 1995].

Many attempts have been undertaken to study the consequences of liver diseases on drug metabolism [Bass and Williams 1988, McLean and Morgan 1991, Morgan and McLean 1995, Paintaud et al. 1996, Rodighiero 1987, 1999]. But because of small sample sizes, frequent lack of precise information on the severity of the liver diseases and/or use of probe drugs whose enzyme (s) were not properly characterized with respect to each metabolic pathway, a difficulty emerges from these studies to collect information relevant for daily therapeutic practice.

In the summary and conclusion of a meeting report published in Br. J. of Clin. Pharm. Reidenberg and Breckenridge [1998] pointed up these drawbacks and defined goals for fu-

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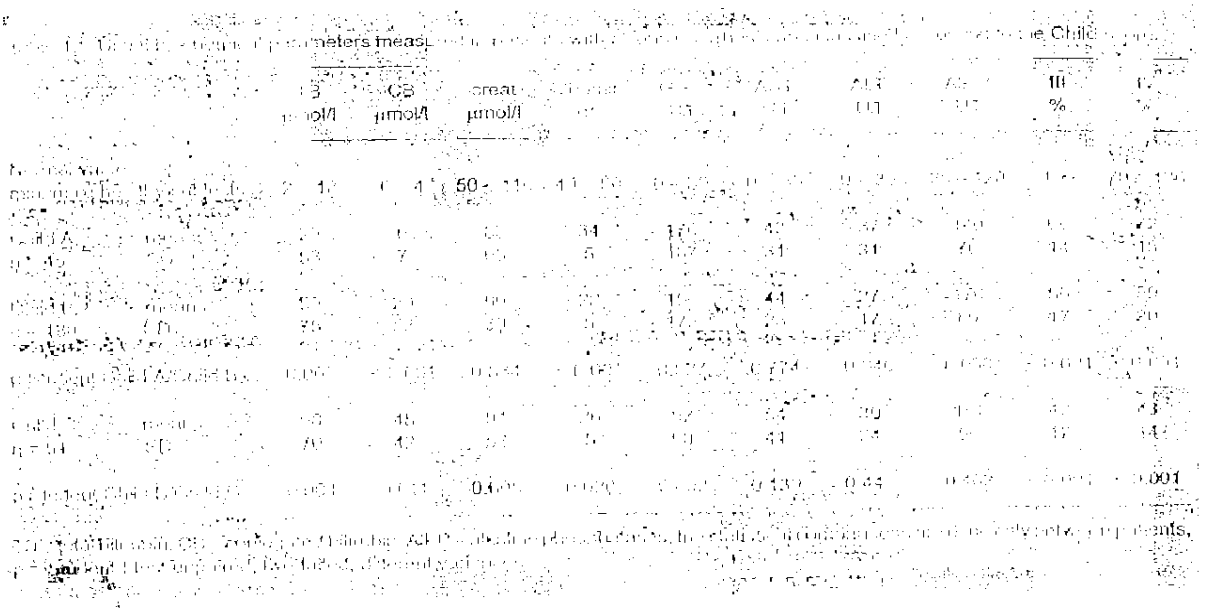

ture research: "To describe the effects of liver diseases on specific pathways of drug metabolism, so that the effects of liver diseases on the kinetics of a new drug, could be accurately predicted after its specific pathway (s) of elimination are known". And even though Bircher [1983] suggested that probe drug pharmacokinetics could be used as a quantitative assessment of liver function, they asked for: "the development of better clinically useful methods of assessing liver function".

Caffeine is a useful and safe probe drug for drug-metabolic studies. It is rapidly and completely absorbed from the gastrointestinal tract, distributed in total body water. It has a low plasma binding, a short half life, a negligible first pass metabolism, a low renal elimination and is nearly totally metabolized in the liver [Arnaud 1987, Bonati and Garattini 1988]. Caffeine-metabolic pathways [Arnaud 1984] and enzymes which catalyze these pathways are known [Fuhr et al. 1996, Gu et al. 1992, Rostamani-Hodjegan et al. 1996].

We used caffeine in vivo as a probe drug in 226 patients with alcoholic cirrhosis to assess, in a large population, the effects of the severity of the disease on the different pathways of caffeine metabolism, and to examine its possible use as a quantitative test of liver function.

Subjects, material and methods

Subjects

Between 1985 and 1999, an hepatic function test using caffeine as a probe drug, has been routinely associated with the usual biochemical data and clinical examinations performed on patients with alcoholic cirrhosis. Based solely on the possibility of finding in the dossier all the data (Table 1) necessary to classify the cirrhotic patients according to the Child Pugh score [Pugh 1973], we selected 226 subjects out of 275 investigated (Table 1).

45 were classified as Child A: 37 men (mean age 58 years; range 44 – 75), 8 women (mean age 52; range 42 – 74). 130 were classified as Child B: 107 men (mean age 54; range 32 – 75), 23 women (mean age 54; range 33 – 73). 51 were classified as Child C: 34 men (mean age 52; range 33 – 66), 17 women (mean age 49; range 33 – 62).

During the same period, caffeine test was performed on 70 healthy subjects: 38 men (mean age 30, range 22 – 60) and 32 women (mean age 31, range 21 – 55). These were members of the department of Clinical Pharmacology, students and healthy volunteers

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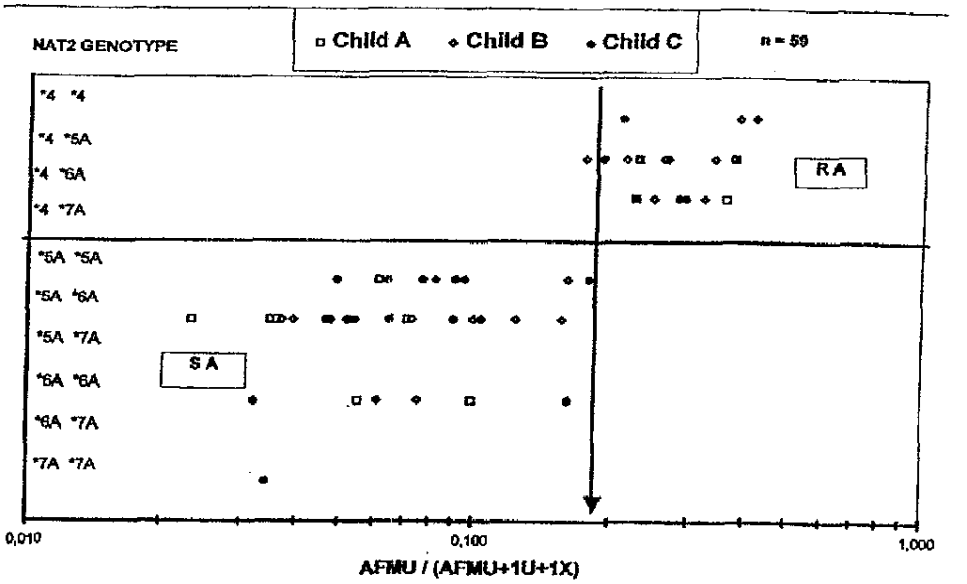

Figure. 1. Relationships between the rapid acetylators (RA) and slow acetylators (SA) phenotypes (NAT-2 index: AFMU/(AFMU+1U+1X) and the NAT-2 genotypes.: homozygous RA: NAT-2 *4 *4; heterozygous RA: NAT-2 *4 *5A, NAT-2 *4 *6A, NAT-2 *4 *7A; homozygous SA: NAT-2 *5A *5A, NAT-2 *5A *6A, NAT-2 *5A *7A, NAT-2 *6A *6A, NAT-2 *6A *7A, NAT-2 *7A *7A, in 59 patients with liver cirrhosis. The vertical line denotes the antimode of the distribution in healthy subjects: AFMU/(AFMU+1U+1X) = 0.180.

who had been selected to participate in phase I pharmacokinetics studies. This sample served as a control group for patients in the 3 groups mentioned above.

Caffeine test and metabolite determinations

Patients were asked to refrain from food, beverages and, if possible, medicines containing methylxanthines from 24 hours before and throughout the 24 hours duration of the test. In the morning, at 8 a.m. after voiding their bladders, they were given 200 mg of caffeine, prepared in the Central Pharmacy of the Hospital, in water. Urine samples were then collected in a plastic jar containing 2 ml of 6 N hydrochloride acid. The containers were gathered, the volume of urine measured and aliquots were transferred into plastic tubes containing 20 mg of ascorbic acid per ml of urine.

Assays of caffeine and caffeine metabolites were performed only if the pH value of the urine in the jar was < 5. The tubes were frozen and maintained at –20° C until analysis, which was performed usually within 3 days after the end of the test. Under these conditions, caffeine metabolites and particularly AFMU were stable enough to allow a quantitative determination by HPLC according to the method described by Grant et al. [1983] using a Waters liquid chromatograph (Waters Chromatography Millipore, Milford, MA, USA) incorporating a 6000 A pump, a Wisp/712 automatic injector, a Beckman Ultrasphere ODS column (4.6 × 150 mm internal diameter); (Beckman Instruments, Inc. Fullerton CA, USA) with a guard column: Bondapack C18, 37 – 50 µm, 20 mm.

In our study the coefficients of variation intra-assay (n = 10) were:

AFMU (4.4 nmol/ml): 2.7%; 37X (6.7 nmol/ml): 4.6%; 1X (14.5 nmol/ml): 5.6%; 137X (7.1 nmol/ml): 2.3%; 3X (7.2 nmol/ml): 6.2%; 1U (8.8 nmol/ml): 6.0%; 7X (7.2 nmol/ml): 5.5%; 13U (3.1 nmol/ml): 5.8%; 13X (1.1 nmol/ml): 4.7%; 17U (8.2 nmol/ml): 5.7%; 17X (6.7 nmol/ml): 3.9%.

The stability of the coefficients of variation and the reproducibility of the test were

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regularly checked according to a routine control procedure implemented in the laboratory. Briefly, regularly repeated intra-assay measurements of variation coefficients, metabolites determination on fresh aliquots from 24 hours pooled urine from healthy subjects caffeine tests were performed.

The following urinary metabolite ratios were used as indices of enzyme activities [Grant et al. 1983, Rostamani-Hodjegan 1996]: CYP1A2: (AFMU+1U+1X)/17U; CYP2A6: 17U/17X; XO: 1U/1X; NAT-2: AFMU/(AFMU+1U+1X).

Blood samples were obtained 24 hours after caffeine intake to measure the residual plasma concentration of caffeine.

Acetylator genotype determination

Genome DNA was prepared from peripheral leucocytes by proteinase K digestion and phenol-chloroforme extraction as described by Neitzel [1986]. The genotypes were subsequently determined by carrying out three separate P.C.R according to the method of Blum et al. [1990]. The primers were designed to detect either the presence of the normal NAT2*4 allele or the NAT2*5A, NAT2*6A and NAT2*7A mutated alleles which prevail in Caucasian population. DNA from subjects with known genotypes were used as negative and positive controls. Genotyping was carried out on 59 patients with alcoholic cirrhosis waiting for a liver transplantation.

Calculation and statistical analysis

Data are presented as mean values ± SD urinary elimination rate of caffeine metabolites, expressed in µM/24h and enzyme activity indices. They are compared by means of the unpaired two-tailed Student's t-test with different variances. Because of the bimodal distribution of the polymorphic enzyme N-acetyltransferase, the rapid acetylators (RA) and slow acetylators (SA) groups are compared separately.

Results

Urinary elimination rates of caffeine and its metabolites (Tables 2, 3, Figure 2)

Compared to healthy subjects, 24-hour total elimination rates of caffeine plus metabolites were significantly decreased according to the severity of the cirrhosis: by one third in the group of patients classified as Child A, by one half in the group of patients classified as Child B and C. Taken individually, in the group classified as Child A only urinary elimination rates of 1U, 1X and AFMU, the final metabolites of caffeine, were significantly decreased. Urinary elimination rates of 17X, 17U, 13X and 37X were not different from that of the controls. Urinary elimination of unchanged caffeine was increased. Finally, urinary elimination of two minor metabolites 7X and 13U was decreased. The metabolism of caffeine was decreased to a large extent in the Child B and C groups as shown by an additional significant increase in the urinary elimination rate of caffeine by its 24-hour residual blood concentration, and by a further decrease of the elimination rates of all metabolites but 37X whose elimination was significantly increased.

Indices of enzyme activities (Table 2)

CYP1A2 index was significantly decreased by one third in the group of patients classified Child A, and by one half in the group Child B without additional decrease in the group Child C.

CYP2A6 and XO indices were not significantly modified in the Child A group when compared to healthy subjects. They were significantly increased in the Child B and C groups.

When compared to healthy subjects, NAT-2 index remained unchanged in SA despite the decreased elimination rate of AFMU. On the other hand, NAT-2 indices were significantly decreased in RA patients classified Child B and C.

Anyway, despite these variations, we found a good relationship between the pheno-

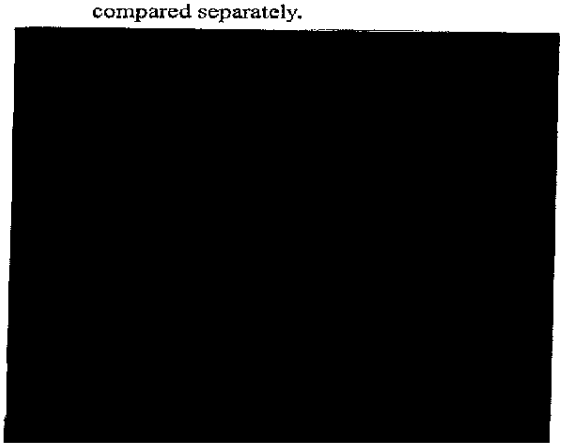

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Table 2. Mean and SD values of 24-hour urinary excretion of caffeine and metabolites in healthy subjects and patients with alcoholic cirrhosis classified according to the Child score.

		1U	1X	17U	17X	7X	3X	13U	37X	137X	13X	Total elim.	Resc	XO	CYP2A6	CYP1A2
							µmol/24h						µg/ml			
Healthy subjects	means	172	146	90	59	73	48	24	23	11	4	719		1.248	1.752	4.734
n = 70	SD	56	67	29	25	45	36	8	18	11	4	157		0.376	0.816	1.904
Child A	means	93	67	78	52	38	36	17	26	33	6	478	2.1	1.674	2.951	2.762
n = 45	SD	68	45	37	33	28	25	10	25	38	6	163	2.0	1.443	1.604	1.786
p Student/healthy subjects		< 0.001	< 0.001	0.084	0.178	< 0.001	0.084	< 0.001	0.518	< 0.001	0.077	< 0.001		0.059	0.252	< 0.001
Child B	means	48	33	53	39	28	36	14	39	62	6	374	7.8	1.916	2.579	1.079
n = 130	SD	34	28	34	44	29	44	21	67	52	9	218	9.6	1.303	2.382	0.931
p Student/healthy subjects		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.052	< 0.001	0.010	< 0.001	0.013	< 0.001		< 0.001	< 0.001	< 0.001
p Student Child A/Child B		< 0.001	< 0.001	< 0.001	0.045	0.031	0.929	0.282	0.063	< 0.001	0.960	0.002	< 0.001	0.324	0.099	0.007
Child C	means	27	21	34	20	28	42	10	53	66	6	311.002	15.2	2.255	3.375	1.674
n = 51	SD	21	24	29	23	27	44	13	91	64	7	201	7.8	2.064	3.892	1.213
p Student healthy subjects		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.413	< 0.001	0.024	< 0.001	0.369	< 0.001		0.001	0.005	< 0.001
p Student Child B/Child C		< 0.001	0.003	< 0.001	< 0.001	0.945	0.479	0.109	0.326	0.581	0.325	0.089	0.114	0.279	0.176	0.580

1U = 1-methylurate, 1X = 1-methylxanthine, 17U = 1-7 dimethyl urate, AFMU = 5-acetylamino-6-formylamino-3-methyluracyl, 17X = 1-7dimethyl xanthine, 7X = 7-methyl xanthine, 3X = 3-methyl xanthine, 13U = 1-3 dimethyl urate, 37X = 3-7 dimethyl xanthine, 137X = caffeine, 13X = 1-3 dimethyl xanthine. Total Elim. = sum of the caffeine and its 10 metabolites 24 hours urinary elimination rates. Res C = residual plasma caffeine concentration 24 hours after 200 mg caffeine intake. N-acetyl transferase, xanthine oxidase, CYP1A2 activity index values in healthy subjects and patients with alcoholic cirrhosis classified according to the Child score. XO = xanthine oxidase index = 1U/1X; CYP2A6 index = 17U/17X, CYP1A2 index = (AFMU + 1U + 1X)/17U.

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Table 3. Because of the genetic polymorphism, the distribution of N-acetyltransferase type 2 index (NAT-2) in the population is bimodal, with rapid acetylators (RA) and slow acetylators (SA). We compared SA and RA separately by the Sudent t test unpaired, two-tailed, with deviations identical to those used in Table 2.

	Slow acetylators			Rapid acetylators		
	AFMU (μM/24h)	AFMU+1U+4X (μM/24h)	NAT-2 ratio	AFMU (μM/24h)	AFMU+1U+4X (μM/24h)	NAT-2 ratio
				1.5	394	0.354
					81	0.094
					28	28
					185	0.319
					72	0.104
					49	19
					0.626	
				0.001	<0.001	0.245
					110	0.281
					74	0.068
					45	45
					0.113	
				0.01	<0.001	0.001
				3	0.001	0.155
					49	0.260
					51	0.057
					16	16
					0.596	
	subjects			0.01	<0.001	<0.001
	Child C			2	0.001	0.233

type and the genotype of NAT-2, whatever the Child score in the patients with alcoholic cirrhosis (Figure 1).

Discussion

Impairment of drug metabolism in liver disease and particularly in alcoholic liver cirrhosis, has been established since the first attempts to study the topic [Howden et al. 1989, McLean and Morgan 1991, Morgan and McLean 1995, Paintaud et al. 1996, Wilkinson and Branch 1984]. However, in cirrhosis reduced drug metabolism is not the sole cause of drug disposition impairment. Malabsorption due to a prolonged orocecal transit and a delay in gastric emptying [Isobe et al. 1994], changes in plasma protein binding [Tillement et al. 1978] and in liver blood flow [Morgan and McLean 1995] drug and metabolite decreased renal clearances [Wensing et al. 1997], are among the factors which may play a role with respect to drug disposition impairment.

In a recent review, Morgan and McLean [1995] emphasized on the difficulties to interpret the published data because, too often, papers included a limited group of patients for whom severity of cirrhosis remained undocumented despite the importance of various factors able to modify drug disposition and associated with severity of the disease.

The pharmacokinetic parameters of caffeine, i.e. complete absorption, low protein binding, small extraction coefficient, renal excretion rate of metabolite more rapid than production in the liver [Bonati and Garattini 1988], support its use as a probe drug for specific hepatic intrinsic clearance measurement [Kalow and Tang 1983].

Scott et al. [1988] reported that caffeine clearance and metabolism were unchanged in mild cirrhosis and that urinary elimination rate of caffeine metabolites was identical in patients and healthy subjects. We observed

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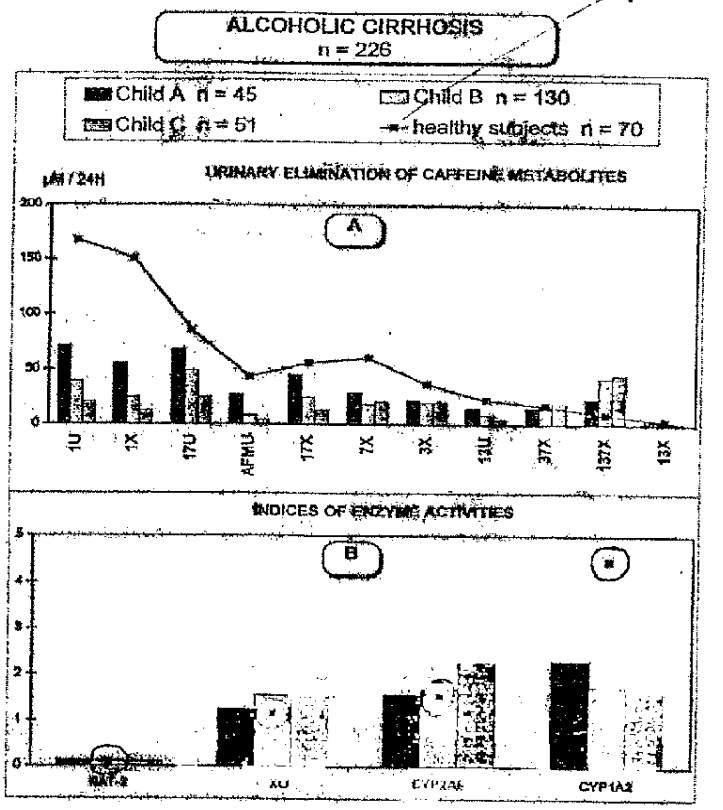

Figure 2. Panel A: Median 24-hour urinary excretion of caffeine metabolites in healthy subjects and in patients with liver alcoholic cirrhosis classified according to the Child score, after a single oral dose of 200 mg of caffeine. 1U: 1-methyl urate, 1X: 1-methyl xanthine, 17U: 1-7dimethyl urate, AFMU: 5-acetylamino-6-formylamino-3-methyluracyl, 17X: 1-7 dimethyl xanthine, 7X: 7-methyl xanthine, 3X: 3-methyl xanthine, 13U: 1-3 dimethyl urate, 37X: 3-7 dimethyl xanthine, 137X: caffeine, 13X: 1-3 dimethyl xanthine. Panel B: Median values of enzyme activity indices. N-acetyl transferase (NAT-2): AFMU/(AFMU+1U+1X). Xanthine oxidase XO: 1U/1X. CYP2A6: 17U/17X, CYP1A2: (AFMU+1U+1X)/17U, in healthy subjects and in patients with alcoholic cirrhosis classified according to the Child score.

(Table 2, Figure 2) a significant decrease of caffeine metabolism as shown by reduced urinary elimination rates of almost all metabolites and high urinary elimination rate of unchanged caffeine, not only in patients with severe cirrhosis classified Child B and C, but also in patients classified Child A. This reduced metabolic capacity was caused by the decrease of the CYP1A2 activity (Table 2, Figure 2) the single enzyme involved in the 3-N-demethylation of caffeine. The validated urinary metabolic ratio (AFMU+1U+1X)/17U was used to measure CYP1A2 activity, rather than those involving 17X whose urinary elimination is renal flow dependent [Rost and Roots 1994, Tang et al. 1994]. Even though the mean value of creatinine did not diverge from the norm in the 3 groups of patients (Table 1), because of the importance of the SD, variations of glomerular filtration even in Child A patients cannot be excluded. Thus, the low level of CYP1A2 activity as main cause of caffeine metabolism impairment, whatever the level of severity of the disease, can be asserted.

However, the 7 and 1 N demethylation of caffeine depends not only on CYP1A2 but also on CYP2E1 [Gu et al. 1992]. Guengerich and Turvy [1991] have shown that CYP1A2 and CYP2E1 were decreased in hepatocyte microsomes from patients with cirrhosis. We do confirm in vivo the decreased activity of CYP1A2. But the increase of 37X and the decrease of 17X urinary elimination rates, only a trend in the group of patients classified A, but significant in those classified Child B and C, suggest a differential effect of cirrhosis which may be less important on CYP2E1 than on CYP1A2. The consequence would be a relative shift of the first steps of caffeine metabolism from the main pathways leading to 17X to a secondary one leading to 37X. The urinary excretion rate of 13X whose production is also CYP1A2 and CYP2E1 dependent was too low to permit the same observation. To confirm the hypothesis, an assay with a more specific CYP2E1 probe drug should be performed.

NAT-2-dependent acetylation produces a minor metabolite of caffeine, AFMU. The urinary metabolic ratio AFMU/(AFMU+1U+1X) is an index successfully used to phenotype healthy subjects and patients [Bechtel et al. 1993, Bendriss et al. 1998, Grant et al. 1984]. In a recent review on drug acetylation and liver disease, Levy et al. [1998] reported that, in cirrhosis, the half-life of isoniazid and the monoacetyl dapsone/dapsone plasma ratio did not show a clear bimodal distribution. Given this drawback, conflicting data were published regarding the prevalence of SA and RA in patients with chronic liver diseases. May et al. [1992] found a greater prevalence of SA in patients with liver cirrhosis, but

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Elyazigi et al. [1995] failed to find any SA prevalence in cirrhotic patients using caffeine urinary metabolic ratio, with a phenotype assignment based on the antimode used in healthy subjects. Similarly, we did not find any clear bimodal distribution (probit plot not shown) of NAT-2 ratio in cirrhotic patients, and we used an antimode value defined in healthy subjects to ascribe the SA or RA phenotype. Comparing phenotype and genotype (Figure 1), all patients were correctly classified, but one heterozygous Child A, RA patient whose ratio was near the antimode where correct phenotype assigment is questionable [Bechtel et al. 1993]. On this basis, for 226 patients with alcoholic cirrhosis, we did not find any difference in the prevalence of SA in cirrhotic patients (64%) compared to healthy subjects (60%).

Radopoulos et al. [1995] and Denaro et al. [1996] reported, both in a group of 11 cirrhotic patients, a decrease in caffeine clearance but an unaltered urinary acetylation ratio. We divided the population of cirrhotic patients into SA and RA groups with enough subjects in each Child group (Table 3). AFMU urinary elimination rate was significantly reduced in relation to the severity of cirrhosis in both RA and SA groups. The sums of AFMU+1U+1X, the three terminal metabolites of caffeine, were identical in RA and SA whatever the Child score (Table 3). In the SA group, the NAT-2 ratio was not different from that of healthy individuals, whereas in RA classified Child B and C there was a significant decrease of urinary acetylation ratios.

Despite the observed differences, compared to the usual laboratory tests, caffeine metabolism, evaluated by urinary elimination rate of its metabolites and indices of enzyme activities, does not bring additional information on the severity of the disease. Related to the Child score, the levels of bilirubine, albumin and factor V (Table 1) were well matched with the decrease of caffeine metabolites elimination (Table 2). Given the large interindividual variability, the association of these two sources of information may help to improve the follow up of a particular patient, and to optimize dosage regimen of prescribed drugs, in particular those with a narrow therapeutic index.

Conclusion

In patients with alcoholic cirrhosis a global decrease of caffeine metabolism is observed, even in patients classified Child A. This does not bring additional information on the severity of the disease in comparison with usual laboratory tests. However, the differential effect on the various enzymes involved in caffeine metabolism is expected to cause a shift from major metabolic pathways to minor ones. This should be taken into account for drugs whose metabolism is of the polygenic regulation type. Because caffeine metabolism is reduced to a larger extent if the disease is severe and given the large interindividual variability, association of a such "caffeine test" with usual laboratory tests might improve the follow up of the patients with alcoholic cirrhosis.

Aknowledgements

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• Rq. for exp ratios ?

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